

CLAIMS

1. A synthetic, soluble, endogenous complex formed from at least one component A and at least one component B, whereby component A comprises a binding domain for extra-cellular surface structures that internalize upon binding of component A of said complex, and component B has a constitutive catalytic kinase activity and effects cell biosynthesis/signaling including cell death after internalization.
2. The complex according to claim 1, whereby the component A is selected from the group of actively binding structures consisting of antibodies or their derivatives or fragments thereof, and/or synthetic peptides such as scFv, mimotopes, and/or chemical molecules such as carbohydrates, lipids, nucleic acids, peptides, vitamins, and/or small molecules with up to 100 atoms with receptor-binding activity such as ligands, in particular single ions, peptidic molecules, non-peptidic molecules, and/or cell surface carbohydrate binding proteins and their ligands such as lectins, in particular calnexins, c-type lectins, f-type lectins, m-type lectins, p-type lectins, r-type lectins, galectins and their derivatives, and/or receptor binding molecules such as natural ligands to the cluster of differentiation (CD) antigens, like CD30, CD40, cytokines such as chemokines, colony stimulating factors, type-1 cytokines, type-2 cytokines, interferons, interleukins, lymphokines, monokines, and/or adhesion molecules including their derivatives and mutants, and/or derivatives or combinations of any of the above listed actively binding structures, which bind to CD antigens, cytokine receptors, hormone receptors, growth factor receptors, ion pumps, channel-forming proteins.
3. The complex according to anyone of claims 1 and 2, whereby component A is selected from the group of passively binding structures consisting of allergens, peptidic allergens, recombinant allergens, allergen-idiotypical antibodies, autoimmune-provoking structures,

tissue-rejection-inducing structures, immunoglobulin constant regions and their derivatives, mutants or combinations thereof.

4. The complex according to anyone of the claims 1 to 3, wherein the component A directs the complex to a target cell comprising the binding partner for the binding structures of claims 2 and 3.
5. The complex according to anyone of claims 1 to 4, wherein component A has higher valency by comprising two or more binding structures selected from anyone of those listed in claims 2 and/or 3.
10. The complex according to anyone of the claims 1 to 5, wherein component B is at least one kinase chosen from the following three classes of kinases: 1. eukaryotic protein kinase (ePK) superfamily, 2. histidine protein kinase (HPK) superfamily or 3. atypical protein kinase (aPK) superfamily.
15. The complex according to claim 6, wherein the ePK is selected from the group of calcium/calmodulin-regulated (CaM) death-promoting kinases, consisting of death-associated protein kinase (DAP-kinase, DAPk), DAP kinase-related protein kinase 1 (DRP-1), also named DAP-kinase 2 (DAPk2), DAP like kinase/Zipper interacting protein kinase (DLk/ZIP-kinase), also named DAP-kinase 3 (DAPK3) and DAP kinase related apoptosis-inducing kinase (DRAK1 and DRAK2) families, the group of Group of calcium/calmodulin-regulated (CaM) death-promoting kinases-like (CAMKL) family, consisting of at least 49 subfamilies, protein kinase AMP-activated alpha 1 catalytic subunit (PRKAA1), protein kinase AMP-activated alpha 2 catalytic subunit (PRKAA2), BRSK1 and BRSK2, CHK1 checkpoint homologue (CHEK1), hormonally upregulated Neu-associated kinase (HUNK), serine/threonine kinase 11 (Peutz-Jeghers syndrome) (STK11), MAP/microtubule affinity-regulating kinase (MARK) 1-4, MARKps 01-30, likely ortholog of maternal embryonic leucine
20. The complex according to claim 6, wherein the ePK is selected from the group of calcium/calmodulin-regulated (CaM) death-promoting kinases, consisting of death-associated protein kinase (DAP-kinase, DAPk), DAP kinase-related protein kinase 1 (DRP-1), also named DAP-kinase 2 (DAPk2), DAP like kinase/Zipper interacting protein kinase (DLk/ZIP-kinase), also named DAP-kinase 3 (DAPK3) and DAP kinase related apoptosis-inducing kinase (DRAK1 and DRAK2) families, the group of Group of calcium/calmodulin-regulated (CaM) death-promoting kinases-like (CAMKL) family, consisting of at least 49 subfamilies, protein kinase AMP-activated alpha 1 catalytic subunit (PRKAA1), protein kinase AMP-activated alpha 2 catalytic subunit (PRKAA2), BRSK1 and BRSK2, CHK1 checkpoint homologue (CHEK1), hormonally upregulated Neu-associated kinase (HUNK), serine/threonine kinase 11 (Peutz-Jeghers syndrome) (STK11), MAP/microtubule affinity-regulating kinase (MARK) 1-4, MARKps 01-30, likely ortholog of maternal embryonic leucine
25. The complex according to claim 6, wherein the ePK is selected from the group of calcium/calmodulin-regulated (CaM) death-promoting kinases, consisting of death-associated protein kinase (DAP-kinase, DAPk), DAP kinase-related protein kinase 1 (DRP-1), also named DAP-kinase 2 (DAPk2), DAP like kinase/Zipper interacting protein kinase (DLk/ZIP-kinase), also named DAP-kinase 3 (DAPK3) and DAP kinase related apoptosis-inducing kinase (DRAK1 and DRAK2) families, the group of Group of calcium/calmodulin-regulated (CaM) death-promoting kinases-like (CAMKL) family, consisting of at least 49 subfamilies, protein kinase AMP-activated alpha 1 catalytic subunit (PRKAA1), protein kinase AMP-activated alpha 2 catalytic subunit (PRKAA2), BRSK1 and BRSK2, CHK1 checkpoint homologue (CHEK1), hormonally upregulated Neu-associated kinase (HUNK), serine/threonine kinase 11 (Peutz-Jeghers syndrome) (STK11), MAP/microtubule affinity-regulating kinase (MARK) 1-4, MARKps 01-30, likely ortholog of maternal embryonic leucine
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zipper kinase (KIAA0175), PAS domain containing serine/threonine kinase (PASK), NIM1, QIK and SNRK, the group of death-domain receptor interacting protein kinase (RIP-kinase) family, consisting of at least six subfamilies, RIP-kinase 1, RIP-kinase 2, RIP-kinase 3 and RIP-kinase 4, ankyrin repeat domain 3 (ANKRD3) and SqK288, the group of multifunctional CaM kinase family, consisting of CaM kinases I, II, including the microtubule affinity-regulating kinases (MARK) and microtubule affinity-regulating kinases-like 1 (MARKL1), CaM kinase IV and CaM kinase kinase subfamilies, the group of dedicated CaM kinases, consisting of Myosin light chain kinase (MLCK), phosphorylase kinase and CaM kinase III, the group of mitogen-activated protein kinase (MAPK) family, consisting of extracellular signal-regulated kinases (ERK), c-JUN NH₂-terminal protein kinases (JNK), nemo-like kinase (NLK) and p38 kinase subfamilies, the group of cyclin-dependent kinase (CDK) family, consisting of the subfamilies, cell cycle related kinase (CCRK), cell division cycle 2 (CDC2), cyclin-dependent kinases (CDK) 1-11, PCTAIRE protein kinase (PCTK) 1-3, PFTAIRE protein kinase (PFTK) 1-2 and cell division cycle 2-like 1 (PITSRE proteins), the group of eukaryotic translation initiation factor 2-alpha kinase 3 (EIF2AK3) family, also named (PEK), consisting of the protein kinase interferon-inducible double stranded RNA (dsRNA) dependent (PKR) subfamily.

8. The complex according to claim 6, wherein the histidine protein kinase is selected from one of the eleven families HPK 1-11.
9. The complex according to claim 6, wherein the aPK is selected from the alpha protein kinase family, consisting of eukaryotic elongation factor-2 kinase (eEF-2k), myosin heavy chain kinase (MHC-kinase), eukaryotic translation initiation factor 2 alpha kinase 1 (E2K1) and channel kinase (Chak1 and Chak2) subfamilies, the group of Fas-activated s/t kinase (FASTK) family, consisting of the FASTK subfamily, the group of protein tyrosine kinase 9 (A6) family, consisting of A6 and protein tyrosine

kinase 9-like (A6r) subfamilies, the group of p21-activated protein kinases (PAK) family, consisting of the three highly conserved isoforms: alpha-PAK (PAK1), beta-PAK (PAK3) and gamma-PAK (PAK2, PAKI), the group of Interleukin-1 (IL-1)-receptor-associated kinase (IRAK) family, 5 consisting of IRAK-1, IRAK-2, IRAK-3 and IRAK-4 subfamilies, or derivatives, mutants or combinations thereof.

10. The complex according to anyone of the claims 1 to 9, whereby the constitutive kinase activity of component B directly activates or inactivates components of cell-regulatory pathways through e.g. phosphorylation, acetylation, methylation, prenylation, and sulfation, thereby altering the function, gene expression, or viability of a target cell, whereby the target cell is defined by the binding of component A to it.
15. 11. The complex according to anyone of the claims 1 to 10, whereby component B comprises DAP-kinase 2 (DAPk2) or a derivative thereof.
12. The complex according to anyone of the claims 1 to 10, whereby component B comprises eukaryotic elongation factor-2 kinase (eEF-2k) 20 or a derivative thereof.
25. 13. The complex according to anyone of the claims 1 to 12, comprising one or more supplementary component S which regulates protein biosynthesis on the transcription and/or translation level, and/or enables purification and/or detection of the complex, and/or facilitates translocation of at least component B into the target cell, and intracellular separation and/or activation of component B, whereby the component S is selected from the group of inducible promoters, leader sequences, affinity tags, His tags, translocation domain, amphiphatic sequences and synthetic pro-granzyme B.
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14. The complex according to anyone of the claims 1 to 13, wherein the components are chemically coupled and/or genetically fused to each other.
- 5 15. The complex according to anyone of claims 1 to 14, having the amino acid sequences of SEQ ID NO: 2, SEQ ID NO: 4 and SEQ ID NO: 6.
- 10 16. A nucleic acid molecule coding for the complex according to anyone of claims 1 to 15 or for individual components thereof for the preparation of such complex, and/or a vector comprising said nucleic acid molecule.
- 15 17. A cell or non-human organism after having been transformed or transfected with the nucleic acid molecule or vector according to claim 16, and/or an *in vitro* translation system's synthesizing the complete complex according to anyone of the claims 1 to 15 or individual components thereof.
- 20 18. The organism or cell according to claim 17, wherby the organism is either a prokaryote, such as *E. coli*, *B. subtilis*, *S. carnosus*, *S. coelicolor*, and/or *Marinococcus sp.*, or a lower eukaryote, such as *Saccharomyces sp.*, *Aspergillus sp.*, *Spodoptera sp.* and/or *P. pastoris*, a higher non-human eukaryote such as a plant and/or an animal, and the cell is a primary or cultivated mammalian cell, such as a freshly isolated human cell or a eukaryotic cell line such as CHO, Cos or 293.
- 25 19. A method for influencing the growth and/or the physiology of the cells according to anyone of the claims 18 and 19, by culturing the cells under conditions supporting the activity of the complex.

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20. A kit comprising the complexes according to anyone of the claims 1 to 15, and/or the nucleic acid molecule and/or the vector of claim 16, and/or the cells and/or non-human organisms of claims 17 or 18.
- 5 21. Use of the complex of claims 1 to 15 and/or the nucleic acid molecule and/or vector of claim 16, and/or the cells and/or non-human organisms of claims 17 or 18, and/or the kit of claim 20 for the preparation of a medicament for the treatment of proliferative diseases, such as cancerous or non-cancerous proliferative diseases, allergies, autoimmune diseases, and/or chronic inflammation.
- 10 22. A medicament comprising the complex according to anyone of the claims 1 to 15, the nucleic acid molecule and/or vector according to claim 16, or the cells or non-human organisms according to either one of claims 18 or 15 19.
- 15 23. Use of the complex according to anyone of the claims 1 to 15, and/or of the nucleic acid molecules and/or vectors of claim 16, and/or of the cells and/or non-human organisms of claims 17 or 18, and/or the the kit according to claim 20 for targeted modulation of cellular signaling pathways.
- 20 24. Use of the complex according to any of the claims 1 to 15, of the nucleic acid molecules and/or vectors of 16, and/or of the cells and/or the non-human organisms of claims 17 or 18, for the development of prognostic, diagnostic, and analytic kinase assays.
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